Original Article

Contribution of various lipid profile parameters in determining creatine kinase-MB levels in unstable angina patients

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Abstract

Context: In India, the correlation of severity of minor myocardial damage with dyslipidemia has rarely been studied in patients of unstable angina (UA). Dyslipidemia is proven to be a major risk factor for developing acute coronary syndrome (ACS) but still there is doubt about the type of lipoproteins involved in causing minor myocardial damage occurring in UA patients of ACS. **Aims:** The aim of our study was to find out the contribution of various types of lipoproteins to predict the severity of minor myocardial damage occurring in the patients of UA. **Settings and Design:** Correlation design was used for the study. A single group of individuals was selected. Data were collected on dependent variable creatine kinase-MB (CK-MB) and independent variables (lipid profile parameters). **Subjects and Methods:** The study comprised fifty patients admitted in cardiac care unit with typical history of UA with electrocardiogram showing no ST-segment elevation. The severity of myocardial damage was assessed from on admission CK-MB levels. The lipid profile was estimated from fasting blood samples of all the patients. **Statistical Analysis Used:** For the purpose of the study, Pearson correlation and multiple linear regression analysis methods were applied. **Results:** The triacylglycerol (TAG), very-low-density lipoprotein (VLDL), total cholesterol/high-density lipoprotein (TC/HDL) showed significant positive correlation whereas HDL was negatively correlating with CK-MB levels. **Conclusions:** The TAG, VLDL, and TC/HDL were found to be significantly affecting the severity of myocardial damage in the patients of UA.

Key words: Acute coronary syndrome, creatine kinase-MB, dyslipidemia, unstable angina

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Introduction

Acute coronary syndrome (ACS) remains the leading cause of mortality in the world, especially in the developing countries, where the incidence of it is doubled in last 3 years. This change in health risk is particularly evident in newer generation, which may be due to changes in dietary habits, physical activities along with genetic, metabolic, and environmental factors. Although it is a global issue, Indian population has very high incidence of ACS even at low levels of many of these risk factors by comparison with Western standards.[1] Initially, it was considered as the problem of modern Indian society but gradually its incidence is increasing also in the rural part of the country. There are no detailed reports, but mortality and morbidity surveys in India indicate that there is significant variation in the prevalence of cardiovascular diseases, which may be due to substantial regional variation

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in lifestyle and dietary habits in the country.[2] We thought of conducting the study in Andhra Pradesh, which is a considered as a part of South India where the burden of the coronary heart disease (CHD) is reported to be greater (>250/100,000) as compared to central India (<100/100,000).[3] As per the recent studies, in last 20 years, there is a fall in prevalence rate of CHD in developed countries but in India, the developed region such as Kerala and Mumbai has the highest rate of CHD in the country.[4]

ACS is classified as unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI) and STEMI depending on occurrence of ST-segment elevation on electrocardiogram. There are many studies proving the role of lipid profile fractions for the development of coronary artery disease (CAD), particularly South Eastern India, but its role in deciding the severity of myocardial damage in UA has rarely been studied.[5,6]

Thus, the objective of this study was to find out the relative contribution of various lipid profile parameters in raising the creatine kinase-MB (CK-MB) levels, which correlate well with mortality and the atherosclerotic plaque burden in the patients of UA with ACS where the extent of damage is usually very minimal.[7-9]

Subjects and Methods

The present study comprised fifty patients admitted to intensive coronary care unit. Males were 36 whereas females were 14 in number. The age ranged from 35 to 65 years with mean age of 50 years. All patients gave informed consent to the study protocol, which was approved by the Institutional Ethical Committee. The patients with NSTEMI and UA were included in the study. The patients with angina pectoris or equivalent type of ischemic discomfort with at least one of the following three features were diagnosed as UA: (1) Being severe and frank pain, (2) occurring at rest and usually lasting >20 min (without medication), and (3) awakens the patient from sleep and it is more severe, prolonged, and frequent than before. The patients with UA showing the evidence of myocardial damage assessed on the basis of elevated cardiac markers like myocardial specific CK isoenzyme (CK-MB), so they were considered as NSTEMI.[5]

Patients presenting with STEMI, thyroid dysfunction, liver disease, renal disease, trauma, sepsis, pulmonary embolism, myocarditis, congestive heart failure, muscular dystrophy, and skeletal muscle injury were excluded from the study.

First, blood sample was collected within 12–24 h after the onset of chest pain in plain vaccutainer and allowed to clot at room temperature for CK-MB estimation. Then serum was separated by centrifugation at 3000 rpm for 10 min. The CK-MB was estimated by immunoinhibition method. The early morning fasting blood sample was collected on day one after admission to estimate different lipid profile parameters.

The serum cholesterol was estimated by cholesterol oxidase phenol aminophenazone (PAP) method, triacylglycerol (TAG) by glycerol-3-phosphate PAP method, low-density lipoprotein (LDL), and serum high-density lipoprotein (HDL) by enzymatic colorimetric method. The ratio of total cholesterol (TC)/HDL and LDL/HDL were calculated manually. For adequate quality control, both normal and abnormal reference control serum solutions and calibrator were run before each batch. All the biochemical estimations were done on an autoanalyzer Humastar 300 (Human Diagnostics, Max-Planck-Ring 21.65205 Wiesbaden, Germany) by using commercially available kits. For statistical analysis, Pearson correlation and multiple linear regression analysis method were applied. Assumptions were tested before applying the statistical techniques.

Results

Assumptions for linear regression model were tested first as follows:

Checking of outliers

Assumption: No outliers. Analysis showed standard residuals, which should not exceed ±3.[10] In the present study, minimum was found −1.43 and maximum 2.97, which fulfilled the assumption of no outliers [Table 1].

Checking independence of data points

Assumption: The data points must be independent. The analysis has shown the Durban–Watson value of 1.43, which fulfills the assumption regarding independence. This value lies in the range of 1–4 whereas a value near to two is considered as appropriate.

Checking normality

Assumption: Distribution of residuals should be normal with mean = 0 and a constant variance [Table 1]. Histogram and normal P-P plot of regression standard residuals also showed that data were normally distributed [Figures 1 and 2].

Table 1: Residual statistics for checking outliers

	Minimum	Maximum	Mean	SD	Number of patients
Predicted value	1.2482	187.6243	44.4000	33.46	50
Standard predicted value	−1.289	4.280	0.000	1.00	50
Standard residual	−1.437	2.975	0.000	0.97	50

Dependent variable – CK-MB: Creatine kinase-MB; SD: Standard deviation

Descriptive statistics including mean, standard deviation, skewness and kurtosis were calcuted in this regard [Table 2].

It is evident that the distribution of the residuals satisfies the normal assumption since the mean is almost 0, which is 0.000 (−2.08E-17) and standard deviation is almost 1 (0.97) [Figures 1 and 2].

Scatter plot for regression standardized predicted value shows no clear pattern [Figure 3]. Hence, it may be concluded that variance was constant. Since assumption for linear regression model has been found satisfactory, linear regression was applied to estimate the effect of lipid profile parameters on CK-MB levels.

By using multiple linear regression analysis, two models were established, first model is established by taking only one variable, i.e., serum TAG and second model established by taking two variables, i.e., serum TAG and serum HDL. Table 3 shows that significant relationship of CKMB level was found with TAG, HDL, very LDL (VLDL) levels, and TC/HDL ratio.

Tables 4 and 5 show two models. In case of the first model, coefficient of correlation (*R*-value - 0.54) shows the relationship between CK-MB and serum TAG. Adjusted R square of 0.28 showed that 28% of CK-MB was explained by serum TAG. F value for this model was found significant at 0.01 levels that justified the usefulness of this model. In case of the second model, *R*-value - 0.65 shows the relationship between CK-MB with serum TAG and serum HDL. Adjusted *R* squaere of 0.39 showed that 39% of CK-MB was explained by serum TAG and serum HDL. *F* value for this model was found significant at 0.01 level that also justified the usefulness of this model. As other parameters contribution was negligible, they were automatically excluded from comparison. In relation to both models, tolerance and variance inflation factor also fulfilled the assumption of colinearity.

The information about the quantification of relationship between the levels of CK-MB and lipid profile parameters is given in Table 6. When TAG is increased by 1 unit, CK-MB increased by 0.434 units when TAG alone is considered but when HDL is also considered along with TAG, 1 unit of HDL was responsible to decreased CK-MB level by 1.93 units. Both the results were highly significant.

Discussion

The analysis showed that out of various lipid profile parameters studied, CK-MB levels were correlating positively with TAG, VLDL, and TC/HDL with very high level of significance (<0.01) whereas LDL/HDL ratio correlated with significance of 0.05. The individual levels of TC and LDL have not shown significant correlation with CK-MB but their ratios with HDL were correlating positively with that of CK-MB levels. This may be due to the fall of TC and LDL levels after acute myocardial infarction noted earlier by various researchers, which could be due to acute phase response associated with up-regulation of LDL receptor activity level.[11,12]

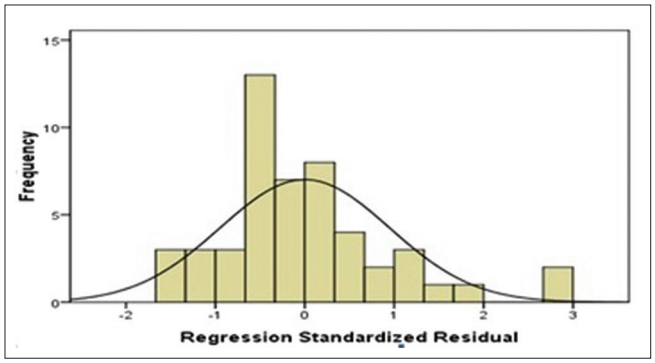

Figure 1: Histogram with normality curve in relation to creatine kinase-MB, standard deviation

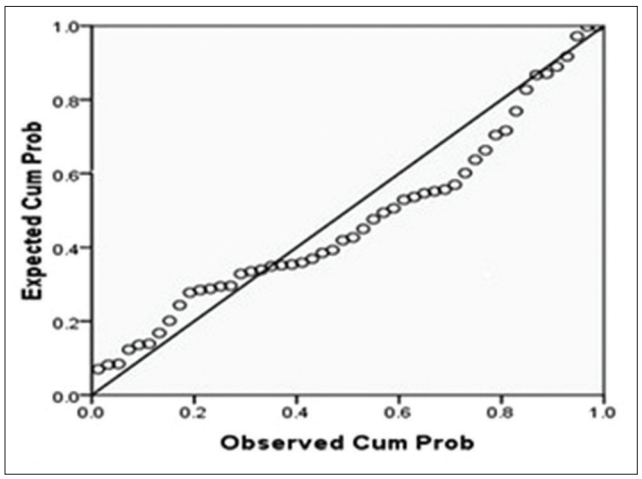

Figure 2: Normal probability-probability plot in relation to creatine kinase-MB levels

Table 2: Descriptive statistics of dependent and independent variables

Measures	CK-MB (U/L)	TC (mg/dl)	TAG (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)	TC/HDL	LDL/HDL
Mean	44.4	187.06	151.16	40.52	109.32	31.1	4.7476	2.754
SD	48.46	40.65	61.36	8.72	29.93	15.25	1.25	0.76
Kurtosis	3.11	0.29	8.19	−1.04	−0.43	13.77	5.15	1.16
Skewness	1.97	0.31	2.44	0.10	0.22	3.34	1.89	0.85

Dependent variable – CK-MB: Creatine kinase-MB; SD: Standard deviation; TC: Total cholesterol; TAG: Triacylglycerol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; VLDL: Very-low-density lipoprotein

Table 3: Multiple correlation regression analysis

	TC	TAG	HDL	LDL	VLDL	TC/HDL	LDL/HDL
r	0.140	0.549	−0.353	−0.021	0.354	0.428	0.234
P	0.167	0.000	0.006	0.443	0.006	0.001	0.051

Dependent variable - TC: Total cholesterol; TAG: Triacylglycerol; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; VLDL: Very-low-density lipoprotein; *r*: Pearson's correlation coefficient; *P*: Level of significance

Table 4: Model summary showing Pearson's correlation between creatine kinase-MB and various lipid profile parameters

Models	*R*	*R* square	Adjusted *R* square	SE of the estimate	Durbin–Watson
TAG	0.549	0.302	0.287	40.90968	1.418
TAG and HDL	0.650	0.422	0.398	37.60118	

Dependent variable - *R*: Coefficient of correlation; TAG: Triacylglycerol; HDL: High-density lipoprotein; SE: Standard error

Table 5: The analysis of variance table of linear regression model in relation to the effect of various lipid profile parameters on creatine kinase-MB levels

Model	Sum of squares	df	Mean square	*F*	Significant
Regression	34,719.12	1	34,719.12	20.745	0.000
Residual	80,332.88	48	1673.60		
Total	115,052.00	49			
Regression	48,601.09	2	24,300.55	17.188	0.000
Residual	66,450.90	47	1413.85		
Total	115,052.00	49			

1. Predictors: (constant) TAG; 2. Predictors: (constant) TAG and HDL. Dependent variable - *F*: Analysis of variance, df: Degrees of freedom, TAG: Triacylglycerol; HDL: High-density lipoprotein

Table 6: Coefficients showing quantification of relationship between the levels of lipid profile parameters and creatine kinase-MB

Model	Unstandardized coefficients		Standardized coefficients (β)	t	Significant*
	B	SE			
(constant)	−21.171	15.515		−1.365	0.179
TAG	0.434	0.095	0.549	4.555	0.000
(constant)	57.532	28.883		1.992	0.052
TAG	0.431	0.088	0.546	4.921	0.000
HDL	−1.931	0.616	-0.347	−3.133	0.003

*Significant at <0.05 level. Dependent variable - CKMB: Creatine kinase-MB; TAG: Triacylglycerol; HDL: High-density lipoprotein; SE: Standard error

In our study, the parameters which contributed maximum in the rise of CK-MB was TAG which alone has given 28.7% contribution whereas decreased HDL levels added 11% to rise of CK-MB levels. Supporting our findings, there are many researchers who have compared the lipid profile parameters in various types of ACS classified as per the severity. Uetani *et al*. who performed intravascular sonography and correlated plaque lipid profile fractions and serum LDL with CK-MB levels proved that CK-MB levels were significantly correlating with severity of the CAD and serum LDL levels.[13] Some researchers like Mehran *et al*. has also reported that CK-MB elevation correlates with coronary artery plaque burden and calcification which are considered to be the principal causes for myocardial ischemic lesions.[9]

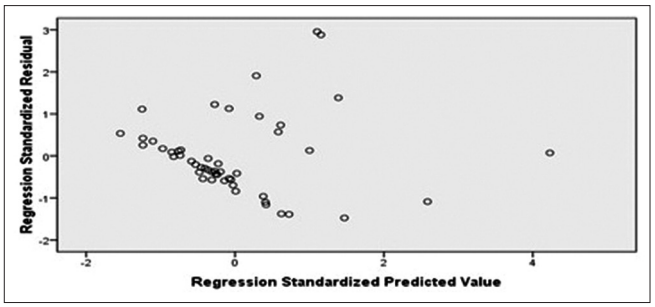

Figure 3: Scatter plot standardized residual versus standardized predicted value, CKMB: Creatine kinase-MB

Rao *et al*. also noted significantly higher serum LDL, VLDL, TAG, and TC levels, and lower HDL levels in STEMI group as compared to age-matched controls.[14] Gruzdeva *et al*. estimated the levels of these lipid profile parameters in STEMI patients and severity of the disease was assessed by the number of vessels involved, found that only LDL levels were significantly correlating with severity of the disease.[15] Similarly, Penalva *et al*., who correlated the lipid profile and severity of CAD in patients of NSTEMI, found that there was significantly higher TC/HDL ratio in the multi-vessel group as compared to single vessel group but as like our study the correlation of severity with LDL levels was not significant.[7]

Unlike our findings, Khan *et al*., who compared the lipid profile factors among UA, NSTEMI, STEMI, and controls, noted the levels of TC, LDL, and HDL were significantly lower in descending order from controls, UA, NSTEMI, and STEMI group as per the severity.[16] Dalager *et al*. who studied the characteristics of the plaques with the help of CT-angiography as per the severity of infarction noted the stabilization of atherosclerotic plaques after receiving course of the antiatherosclerotic drugs (statins) in UA/NSTEMI patients whereas the calcified plaque lesions in STEMI patients were noted to be progressive.[17] However, the researchers like Djordjevic *et al*. could not found any difference in the lipid profile factors among statin-treated and untreated group in NSTEMI as well as STEMI patients.[18]

Conclusion

As it was analyzed that among various lipid profile parameters TAG, VLDL and TC/HDL are the inportant risk factors to cause minor myocardiol damage in unstable angina, converting it to myocardial infarction. So it can be concluded that the

strict monitoring of these factors may be useful in limiting the minor myocardial damage in these casees.

Acknowledgment

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Conflicts of interest

There are no conflicts of interest.

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